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1. Your reference	HEWF\P18474GB
2. Patent application number *(The Patent Office will fill in this part)*	9810949.9
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Hewlett Healthcare Limited No 1 Mill The Wharf Shardlow Derby DE72 2GH United Kingdom
Patents ADP number *(if you know it)*	7207712001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4. Title of the invention	FORMULATION
5. Name of your agent *(if you have one)*	ERIC POTTER CLARKSON
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	PARK VIEW HOUSE 58 THE ROPEWALK NOTTINGHAM NG1 5DD
Patents ADP number *(if you know it)*	1305010

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

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Claim(s)	3
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Priority Documents	0
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	NO
Request for preliminary examination and search *(Patents Form 9/77)*	NO
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson — Date

ERIC POTTER CLARKSON — 21 May 1998

12. Name and daytime telephone number of person to contact in the United Kingdom: 0115 9552211

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FORMULATION

The present invention concerns formulations for the topical administration of drugs.

Sodium cromoglycate is known to have beneficial effects in the treatment of atopic conditions, particularly asthma. Some positive results have been obtained in clinical trials addressing its efficacy with regard to atopic dermatitis (also known as eczema or atopic eczema) and associated skin disorders.

Atopic dermatitis is an inflammatory skin disorder, which is particularly prevalent amongst the paediatric population, affecting up to 10% of the paediatric population. It is characterised by extreme itching, a chronic relapsing course and specific distribution around the body. There is usually a family history of allergy and the condition starts in early infancy.

Typical treatment regimes are to use simple emollients or topical corticosteroids. These are the mainstay of treatments for these conditions. Long-term use of topical corticosteriods may have undesirable side effects, particularly in children.

Topical preparations containing sodium cromoglycate have been attempted (ointments, aqueous solutions and creams) but their clinical effect has been disappointing. Expectations of an effect have been high due to the known and clearly demonstrated effect of sodium cromoglycate in the treatment of asthma, and the known relationship of this condition to atopic dermatitis.

The lack of clinical efficacy from topical preparations attempted to date may be due to low bioavailability of sodium cromoglycate in the dermis, which may arise from poor penetration of the skin. Sodium cromoglycate is likely to have poor skin penetration properties arising from its extremely polar nature.

In 1977 Haider (1) published the results of a 12 week, placebo-controlled, double-blind trial of 10% sodium cromoglycate in white soft paraffin in 21 children with atopic dermatitis. The children were aged 4 months to 14 years and the sodium cromoglycate treated group showed significant improvement in inflammation and itching. Three further trials were published using this formulation (2,3,4). None of these showed any clear benefits of sodium cromoglycate. Thirumoothy *et al* (2) reported on the use of the same formulation in 11 patients aged 13 to 38 years; Croner *et al* (3) reported on 19 patients aged 2 to 16 years and Zachariae *et al* (4) on 35 patients aged 2.5 to 15 years. The only positive feature of these trials was a significantly reduced use of topical corticosteroids in the sodium cromoglycate treated group in the trial by Croner *et al*. One possible explanation of the difference between the results of the trial by Haider may have been the atopic status of the patients selected. Haider's patients were all atopic which was not the case in the other trials. Haider published further results in 1979 (5) but in this case a corticosteroid cream was sometimes combined with sodium cromoglycate in the initial stages of treatment.

Initial laboratory and challenge studies failed to provide any positive support for the use of topical sodium cromoglycate. Work carried out in support of the use of sodium cromoglycate in the treatment of asthma had hypothesised that the main pharmacological effect of the drug is to inhibit

the release of inflammatory and chemotactic mediators from mast cells in the bronchial mucosa. The first experiment relevant to the skin, by Pearce *et al* (6), showed that sodium cromoglycate did not inhibit IgE dependent histamine secretion in human skin. This finding was supported by *in vitro* experiments by Clegg *et al* (7), who measured histamine release from human skin slices and Okayama *et al* (8) who measured mediator release from dispersed skin mast cells. It has been suggested that the mast cells in the skin differ from those in the lung and are not sodium cromoglycate responsive.

More recently, however, Crossman *et al* (9) showed that intradermal sodium cromoglycate, *in vivo,* inhibits both substance P and neurokinin B induced wheal in the skin of human subjects and Walsh (10) has shown that sodium cromoglycate inhibits both the release of the cytokine TNFα from mast cells in the skin and the expression of the adhesion molecules CD62E and CD54 in human skin slices irradiated with ultraviolet B. The work by Crossman *et al* resulted in a commentary in the *Lancet* (11) and subsequent correspondence (12) on the likely mode of action of the drug in the skin.

Initial *in vivo* challenge experiments in the skin of human subjects were variable. Ting *et al* (13), was unable to demonstrate any inhibitory effects on the immediate skin reaction to antigen. Van Bever *et al* (14) demonstrated an effect an codeine reactivity but not histamine reactivity and a non-significant effect on antigen reactivity. Grönneberg *et al* (15) showed an inhibition of the late response but not the immediate response to challenge with anti-IgE. More recently, Kimata and Igarashi, (16) and Phillips *et al.* (17) have shown that topical sodium cromoglycate inhibits antigen induced wheal and flare reaction in the skin of human subjects.

Despite the conflicting results of these studies it would seem that sodium cromoglycate may well have an effect on antigen mediated reactions in the skin of humans and that these effects are relevant to its potential clinical efficacy in conditions such as atopic dermatitis. It can also be surmised that any clinical effect is likely to be dependent upon the formulation used achieving good penetration of the skin in order to get to the relevant cells and receptors in the dermis.

In the early 1980's it was shown that the formulation used by Haider was unlikely to achieve good skin penetration and Fisons developed a 4% oil in water cream formulation which had better skin penetration in model experiments. This was used in a clinical trial programme of which 3 trials were published (18, 19, 20). Only one of these trials by Arianayagam *et al* (20) showed positive effects. In this study, which involved nineteen adults aged 16-65 years and twenty-seven children aged 2-14 years a significant effect was seen on the total eczema score after 9 and 12 weeks of treatment. It was also shown that the greatest effect was seen in those subjects with a Total Serum IgE of <500 U/ml. However the skin penetration of this formulation was relatively poor with the calculated bioavailability of the applied dose ranging from 0.01% to 2.75%. This compares to a bioavailability of 10-15% when the drug is administered by inhalation in the treatment of asthma (21).

In 1990 Kimata and Igarishi (22) published a 4 week, placebo-controlled, double-blind trial of 1% aqueous solution of sodium cromoglycate. After application of the aqueous solution the skin was occluded with white soft paraffin. The patient population was 45 children aged 6 months to 3 years. All had moderate to severe atopic dermatitis with Total Serum IgE levels ranging from 100 to 8600 U/ml. The sodium cromoglycate treated

group exhibited significant benefits on the skin after one week's treatment and on the itch and sleep disturbance after two weeks. This same group has subsequently published two further studies. Kimata and Hiratsuka (23) and Hiratsuka *et al* (24). In the trial by Kimata and Hiratsuka, which was conducted in children aged 4 to 14 years, both sodium cromoglycate and placebo treated groups received the antihistamine, oxatomide. However only the sodium cromoglycate treated group showed significant clinical benefits. Significant beneficial effects were seen in the sodium cromoglycate group after one weeks treatment. In this study there were also significant reductions in the serum levels of eosiniphilic cationic protein (ECP) and serum histamine in the sodium cromoglycate treated group. In an additional series of experiments using the blood of the treated patients it was shown that sodium cromoglycate significantly inhibited the spontaneous production of IgE antibodies from peripheral blood mononuclear cells. The third study (24) compared topical sodium cromoglycate with topical beclomethasone dipropionate in 43 children aged 5 to 15 years. Both treatments gave comparable clinical benefits but differed in the effects on spontaneous IgE production by B lymphocytes with a significant inhibition in the sodium cromoglycate group and a significant increase in the topical beclomethasone dipropionate group. These effects on IgE production by human B lymphocytes have also been demonstrated in *in vitro* experiments (25, 26). Whether or not they have any clinical relevance remains to be determined but it suggests that for long-term treatment sodium cromoglycate may be the preferred drug.

The results of topical sodium cromoglycate in atopic dermatitis are extremely variable. This may be result of the different formulations, or concentrations used or the patient population selected or a combination of all three. The concentration used have ranged from 1% to 10% and the

formulations include aqueous solution, creams and ointments. The most positive results have been seen in relatively young children (Range 6 months to 7 years) who are strongly atopic (Serum IgE >2SD from normal).

It is also probable that adequate skin penetration of the drug is an essential pre-requisite of clinical efficacy in order for the drug to attach to the receptors responsible for the allergic inflammation and itch. Sodium cromoglycate is an extremely polar compound and will have poor penetration of skin and mucous membranes. Little is known about its absorption through the skin in patients apart from the formulation used by Ariyanayagam *et al* which gave relatively low levels of absorption. Hiratsuka *et al* were unable to detect any sodium cromoglycate in the blood using a radioimmunoassay after applying an aqueous solution of the drug but it would seem unlikely that the drug was not absorbed in view of the demonstrated effects on B cell activity and on cytokine release. Sodium cromoglycate is not metabolised and is rapidly removed from the blood and the levels may have been below the level of detection. Urinary levels over time are probably a better measure of bioavailability. Haider encouraged his patients to rub the ointment into the skin (personal communication) which may have increased the penetration.

At the publication of the first Japanese trial the journal carried an editorial (28) which stated "*Given the frequent adverse effects of therapeutic alternatives, it certainly seems worth pursuing the potential benefits of topical cromolyn solution. ... An effective, safe new drug to be used in the treatment of this troublesome disease would be very welcome.*"

There is therefore a long-felt interest in and need for the development of an acceptable vehicle that allows adequate skin penetration of sodium cromoglycate, for use in the treatment of atopic dermatitis. So far a suitable vehicle has not been found, despite much interest in the area. Such a vehicle may be useful in a product that may fit as a maintenance treatment, particularly in children, between simple emollients and topical corticosteroids which at present are the mainstay treatment for this condition (27).

Ariyanayagam *et al* (20), for example, report that Bodor *et al* (1980; *Int J Pharmaceut* 7, 63) have produced a series of lipophilic pro-drugs in an attempt to improve the bioavailability of sodium cromoglycate, with encouraging results.

As discussed above, oil-in-water emulsions comprising sodium cromoglycate (or the related cromone nedocromil sodium) are known. Some of these emulsions further comprise anionic surfactants. None comprise amphoteric surfactants, nor is the use of amphoteric surfactants suggested. None comprise alkoxylated cetyl alcohol, a substance used as a water soluble surface active emollient in personal care products.

GB 2 202 145 B, for example, describes several topical formulations of nedocromil sodium (sodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylate), including an oil-in-water emulsion.

Ishikura *et al* (1987) *Drug Design & Delivery* **1**, 285-295 describes the use of amphoteric surfactants in improving percutaneous uptake of diltiazem hydrochloride (used as an example of a cationic water soluble drug) from

water-soluble films. Whilst investigation of uptake of sodium cromoglycate (used as an example of an anionic water soluble drug) was also reported in the paper, the effect of the amphoteric surfactants on scg uptake was not suggested or tested. There is no suggestion that amphoteric surfactants would be of benefit in emulsions.

The present work surprisingly shows that a oil-in-water emulsion comprising an amphoteric surfactant, alkoyxlated cetyl alcohol and a polar drug, for example, sodium cromoglycate may be formed. The emulsion is stable, and an effective amount of the drug may penetrate the skin of a patient when the emulsion is applied topically. The emulsion may be useful in the treatment of skin disease such as atopic dermatitis.

The emulsion of the invention has the unexpected benefit that it produces a stable emulsion of sodium cromoglycate with advantageous skin penetration properties. The proposed combination of ingredients, particularly the amphoteric surfactant and alkoxylated cetyl alcohol, may promote the skin penetration of sodium cromoglycate.

The emulsion of the present invention avoids anionic or cationic substances and provides a stable emulsion comprising the polar substance sodium cromoglycate. The polarity of sodium cromoglycate may limit the stability of known emulsions. The amphoteric surfactant may assist in overcoming this problem and may also assist the skin penetration of the sodium cromoglycate. Use of alkoxylated cetyl alcohol and an amphoteric surfactant in combination may be particularly beneficial in producing a stable and effective emulsion comprising a polar drug, for example sodium cromoglycate or nedocromil sodium.

Thus, a first aspect of the invention is an emulsion comprising an amphoteric surfactant, an alkoxylated cetyl alcohol and a polar drug.

It is preferred that the emulsion is an oil-in-water emulsion.

By polar drug is meant a compound which may be used as an active ingredient in a medicament that is water-soluble and ionises on solution in distilled water at 25 °C. By water-soluble is meant that the compound may be dissolved in distilled water at 25 °C at a ratio of compound to water (weight to volume, or volume to volume if the compound is a liquid) of at least 1 to 10000, 1 to 1000, 1 to 100, 1 to 30, 1 to 10, 1 to 1 or 1 to less than 1. It is preferred that the polar drug is an anionic polar drug, for example a chromone, such as nedocromil sodium or sodium cromoglycate. Most preferably, the drug is sodium cromoglycate.

The drug may be useful in treating skin disease or may be a drug that is useful when administered transdermally.

The drug, for example sodium cromoglycate, may constitute from 0.01 to 20% w/v, preferably 0.1 to 20% w/v, still more preferably 1 to 10% w/v, most preferably about 7.5% w/v of the emulsion.

It is preferred that the emulsion is stable. By this is meant that separation of the oil and water phases is not detectable by visual inspection after a period of at least one day, preferably one week, still more preferably one month, yet more preferably six months or a year after manufacture when stored at 15 °C to 30 °C. Storage may be at, for example, 22 °C.

The term "amphoteric surfactant" is well known to those skilled in the art. Such surfactants (which may also be known as ampholytic surfactants) possess at least one anionic group and at least one cationic group, and can therefore have anionic, non-ionic or cationic properties depending on the pH. If the isoelectric point of the molecule occurs at pH7, the molecule is said to be balanced. Amphoteric surfactants may have detergent and disinfectant properties. Balanced amphoteric surfactants may be particularly non-irritant to the eyes and skin.

It will be appreciated that the emulsion should not contain ingredients that may cause irritation to the skin, even on prolonged use. Compounds to which sensitisation may occur should be avoided. Thus, balanced amphoteric surfactants may be preferred.

The pH of skin is about 4.5. In order to avoid irritation to the skin, a pH that is slightly acidic ie to the acid side of neutral is preferred, for example a pH between about 4.5 and about 7.0. For example, the emulsion may be manufactured to a pH of 6.0, for example using sodium dihydrogen orthophosphate as the buffer agent.

Examples of amphoteric surfactants include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, dodicin, pendecamaine or long-chain betaines, Nikkol AM101® (2-alkyl-*N*-carboxymethyl-*N*-hydroxyethyl imidazolinium betaine), Nikkol AM310® (lauryldimethylaminoacetic acid betaine), Nissan Anon #300 (12 w/v% alkyldiaminoethylglycine hydrochloride, 3 w/v% alkyldiethylenetriaminoglycole hydrochloride; Inui Shouji Co, ADG), C31G (a mixture of alkyl betaines and alkyl amine oxides), N-tetradecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate) or cocamidopropyl betaine.

Any of these may be used, but cocamidopropyl betaine may not be preferred as instances of allergy to this compound, when used in shampoo, have been reported (De Groot *et al* (1995) *Contact Dermatitis* **33(6)** , 419-422).

It will be appreciated that an amphoteric surfactant may be supplied (as an "amphoteric surfactant" or amphoteric sufactant preparation) packaged or compounded with other substances by the manufacturer, and that references to an amphoteric surfactant encompass an amphoteric surfactant alone and a preparation supplied as an amphoteric surfactant by the manufacturer. It is preferred that the amphoteric sufactant is a carboxylated imidazoline derivative. It is particularly preferred that the amphoteric surfactant is disodium coacoamphodiacetate. It is still more preferred that the disodium coacoamphodiacetate is packaged or compounded with lauryl sulphate and hexylene glycol, as is known to those skilled in the art.

It is particularly preferred that the amphoteric surfactant preparation has the following composition:

disodium coacoamphodiacetate	14%w/w
sodium lauryl sulphate	12.5%w/w
hexylene glycol	7%w/w
sodium chloride	3.9%w/w
lauryl alcohol	1.0%w/w
hydrochloric acid	1.0%w/w
sodium sulphate	0.25%w/w
formadehyde	0.03%w/w
water	to 100%w/w

Such a preparation may be Miracare 2MCA/E™, supplied by Rhône-Poulenc Chemicals, Poleacre Lane, Woodely, Stockport, Cheshire SK6 1PQ.

The amphoteric surfactant may be incorporated in the water phase of the oil-in-water emulsion. This may assist skin penetration by the sodium cromoglycate and may hold the emulsion stable. In the absence of an amphoteric surfactant, the emulsion may break down over a period of 24 hours into two phases, ie the oils will separate and float to the surface. The amphoteric surfactant may constitute from 0.05 to 20% weight to volume (w/v) of the emulsion, preferably 0.1% to 10% w/v, still more preferably 1 to 5% w/v, most preferably about 2% w/v of the emulsion. It will be appreciated that the above proportions may refer to an amphoteric surfactant alone or to an amphoteric surfactant preparation, as described above, for example to a preparation of disodium coacoamphodiacetate containing laurylsulphate and hexylene glycol, such as Miracare 2MCA/E™. Preferably, the proportions refer to an amphoteric surfactant preparation. The amphoteric surfactant component may constitute from 0.007 to 2.8% w/v, 0.014 to 1.4% w/v, 0.14 to 0.7% w/v or most preferably 0.28% w/v of the emulsion.

It will be appreciated that when determining the percentage weight to volume of an ingredient of the emulsion, or a solute to solvent, the weight in grams of the ingredient is compared with the volume in millilitres (ml) of the prepared emulsion.

The term alkoxylated cetyl alcohol encompasses polypropoxylated cetyl alcohol, the chemical description given for Procetyl AWS *in Gardner's Chemical Synonyms and Trade Names*, ninth edition. Alkoxylated cetyl

alcohol may be obtained from Croda Chemicals Ltd, Cowick Hall, Snaith, Goole, North Humberside, DN14 9AA. It is marketed as "Procetyl AWS".

The alkoxylated cetyl alcohol may constitute from 0.1 to 20% w/v, preferably from 0.1 to 10% w/v, still more preferably from 0.5 to 4% w/v of the emulsion and most preferably 1% w/v of the emulsion.

It will be appreciated that the critical ingredients of the emulsion are the amphoteric surfactant, alkoxylated cetyl alcohol, the drug component (for example, sodium cromoglycate), water and an oil phase. Suitable components of the oil phase will be known to those skilled in the art, and the following description is not limiting.

It is preferred that the components of the emulsion are chosen such that the emulsion is acceptable to a patient using it. For example, it should not be too greasy. Reference 18 sets out some desirable characteristics of preparations for treating atopic dermatitis.

The oil phase may comprise liquid paraffins, white soft paraffin, glycerol monostearate, non-ionic emulsifying wax, for example sorbitan tristearate, benzyl alcohol and/or isopropyl myristate. These terms are well known to those skilled in the art. Isopropyl myristate is an example of an emollient. Glycerol monostearate is an example of an emulsifying agent. Benzyl alcohol is an example of a preservative and a mild local anaesthetic.

Liquid paraffins may provide from 0.1% to 30% w/v, preferably 1% to 20% w/v, still more preferably 5% to 15% w/v and most preferably about 10% w/v of the emulsion.

White soft paraffin may provide from 0.1% to 30% w/v, preferably 1% to 20% w/v, still more preferably 2% to 15% w/v and most preferably about 5% w/v of the emulsion.

Glycerol monostearate may provide from 0.1 to 10% w/v, preferably 0.5% to 5% w/v, still more preferably 1% to 3% w/v, most preferably 2% w/v of the emulsion.

The nonionic emulsifying wax, for example sorbitan tristearate, may provide from 0.1 to 10% w/v, preferably 0.5 to 5% w/v, still more preferably about 2% w/v of the emulsion.

Isopropyl myristate may provide from 0.1 to 10% w/v, preferably 0.5 to 5% w/v, still more preferably about 2% w/v of the emulsion.

Benzyl alcohol may provide from 0.001 to 5% w/v, preferably from 0.01 to 1.0% w/v, still more preferably about 0.2% w/v of the emulsion.

The aqueous phase comprises water and the drug. It may further comprise one or more preservatives. Disodium edetate (EDTA) and Triclosan (5-chloro-2(2,4-dichlorophenoxy)phenol) are suitable compounds with preservative properties. The drug may be in solution in the aqueous phase.

Disodium edetate may provide from 0.001 to 5% w/v, preferably 0.01 to 1% w/v, still more preferably about 1% w/v of the emulsion.

Triclosan (5-chloro-2(2,4-dichlorophenoxy) phenol) may provide from 0.001% to 5% w/v, preferably 0.01% to 1.0% w/v, still more preferably about 0.2% w/v of the emulsion.

The emulsion may consist essentially of the components listed below, preferably in substantially the quantities listed below. It is preferred that the drug is sodium cromoglycate or nedocromil sodium, most preferably sodium cromoglycate.

sorbitan tristearate 2.0%
glycerol monostearate 2.0%
light liquid paraffin 10.0%
white soft paraffin 5.0%
isopropyl myristate 3.0%
drug 7.5%
disodium edetate 0.1%
amphoteric surfactant 2.0% (for example disodium coacamphodiacetate, which may be compounded with lauryl sulphate and hexylene glycol, for example Miracare 2MCA/E™)
alkoxylated cetyl alcohol 1.0%
triclosan 0.2%
benzyl alcohol 0.2%
purified water 67.0%

An emulsion of the invention may be prepared by methods well known to those skilled in the art. For example, it may be prepared by heating the oils to about 70 °C, then adding them steadily to the water phase (also at or about 70 °C) with good stirring, and then allowing the emulsion to cool.

A further aspect of the invention is a stable oil-in-water emulsion comprising sodium cromoglycate, wherein when the emulsion is applied to skin an amount of sodium cromoglycate penetrates the skin that is sufficient to produce a demonstrable effect in the treatment of atopic dermatitis/eczema.

The amount of sodium cromoglycate that penetrates skin may be measured by techniques well known to those skilled in the art, some of which are mentioned above. Methods include *in vitro* measurements on skin biopsies (which may be human or animal, preferably rodent, still more preferably hairless rat skin) or *in vivo* measurements. For example, the presence of sodium cromoglycate in plasma or urine following topical application to a human or experimental animal (for example rat or rabbit) may be measured. Such measurements are described in Ishikura *et al* (1987) cited above, and Ariyanayagam *et al* (20). Sodium cromoglycate may be quantified by techniques of analytical chemistry, for example high performance liquid chromatography (HPLC).

Effectiveness of the emulsion may be measured in animal models of atopic dermatitis, or in clinical trials on humans. Preferably it is measured in humans.

Patients having atopic dermatitis may be diagnosed by criteria known to the skilled person. For example, patients may be diagnosed by a general medical practitioner recognising the effect of atopic eczema on the surface of the skin. Several sets of criteria for diagnosis have been proposed in order to assist in achieving consistency between studies of the condition ((29) and Williams *et al* (1996) *B J Dermatol* **135**, 12-17). The criteria

discussed in Williams *et al* include: a history of an itchy skin plus three or more of : (i) a history of rash in the skin creases (folds of elbows, behind the knees, fronts of ankles or around the neck); (ii) a personal history of asthma or hay fever; (iii) a history of generally dry skin in the last year; (iv) onset under the age of 2; and (v) visible flexural dermatitis as defined by a photographic protocol.

The criteria by which an effect on atopic dermatitis may be judged are set out in reference 29.

It may be necessary to select patients on the basis of the level of circulating IgE. Suitable IgE tests include an *in vitro* total IgE test and an *in vitro* specific IgE test, for example the UniCAP Total (or Specific) IgE tests sold by Pharmacia & Upjohn, which use the Allergen ImmunoCAPs as the allergen reagent.

It may be desirable or necessary for patients to be screened according to their IgE levels before treatment with sodium cromoglycate is undertaken. More specifically, patients with total serum IgE levels below 150 iu/ml may be less likely to respond to the treatment.

A further aspect of the invention is a method of treatment of a skin disease or condition wherein a drug is applied to the skin of an individual affected by the disease or condition in a formulation comprising alkoxylated cetyl alcohol and/or an amphoteric surfactant.

It is preferred that the drug is sodium cromoglycate or nedocromil sodium.

A further aspect of the invention is the use of an alkoxylated cetyl alcohol and/or an amphoteric surfactant in the manufacture of a medicament for the treatment of a skin disease or condition.

In the following aspects of the invention , it is preferred that the emulsion of the invention comprises sodium cromoglycate or nedocromil sodium.

A further aspect of the invention is a method of treatment of a skin disease or condition comprising applying an emulsion of the invention to the skin of an individual affected by the disease or condition.

A still further aspect is the use of an emulsion of the invention in a method of treating a skin disease or condition.

A still further aspect of the invention is the use of an emulsion of the invention in the manufacture of a medicament for the treatment of a skin disease or condition.

It is preferred that the skin disease or condition is a disease of humans, but may also be one that affects other mammals, for example cats, dogs or horses. The disease or condition may be any in which skin mast cells and/or delayed (cellular) hypersensitivity reactions and/or inflammation is thought to be involved.

It is preferred that the disease or condition is atopic dermatitis or eczema, but it may also be contact sensitivity, psoriasis, drug sensitivity reactions, apthous ulcers, Behçet's syndrome, pemphigus, urticaria, urticaria pigmentosa, pyroderma gangrenosum, chronic skin ulcers, ulcers associated with Crohn's disease, burns, insect stings/bites, herpetic

infections, systemic sclerosis (systemic scleroderma), morphoea (circumscribed or localised scleroderma) and dermal nodular fibrosis.

The emulsions of the invention comprising sodium cromoglycate or nedocromil sodium, may also be useful in the treatment of sunburn or in sunscreen preparations. They may also be useful in cosmetic preparations, for example anti-ageing creams.

The emulsion may be packaged or presented in any convenient way. For example, it may be packaged in a tube, tub, bottle or pressurised aerosol, using techniques well known to those skilled in the art and as set out in reference works such as *Remmington's Pharmaceutical Sciences* 15th Ed, Mac Publishing. It is preferred that it is packaged in such a way as to minimise contact of the unused emulsion with the environment, in order to minimise contamination of the emulsion both before and after the container is opened. It is particularly preferred that the emulsion is packaged in a pressurised aerosol container.

It will be appreciated that the emulsion may have the appearance of a cream or a lotion.

The emulsion may be applied topically to affected areas or prophylactically to unaffected areas. The emulsion may be applied as directed by a physician. For example, the affected area may be rubbed, for example for at least about 5 minutes, to apply the emulsion, in order to encourage absorption of the drug. The emulsion may be applied once or twice a day, or at greater or lesser intervals, depending upon the needs of the patient, as determined by the patient or a physician.

The invention will now be described by reference to the following, non-limiting, examples.

Example 1: preparation of an oil-in-water emulsion comprising sodium cromoglycate

The following substances are combined to form an emulsion. The percentages refer to percentages w/v of the final emulsion.

Group A

sorbitan tristearate	2.0%
glycerol monostearate	2.0%
light liquid paraffin	10.0%
white soft paraffin	5.0%
isopropyl myristate	3.0%
benzyl alcohol	0.2%

Group B

sodium cromoglycate	7.5%
disodium edetate	0.1%
amphoteric surfactant	2.0%(for example disodium coacamphodiacetate, which may be compounded with lauryl sulphate and hexylene glycol, for example Miracare 2MCA/E™)
alkoxylated cetyl alcohol	1.0%
triclosan	0.2%
purified water	67.0%

The emulsion is prepared by heating the oils (compounds in group A) to about 70 °C, then adding them steadily to the water phase (compounds in

Group B; also at or about 70 °C) with good stirring, and then allowing the emulsion to cool.

Example 2: clinical trial of efficacy of the emulsion comprising sodium cromoglycate in the treatment of atopic dermatitis

Patients for the clinical trial may be selected on the basis of a diagnosis of atopic dermatitis, or on the basis of a diagnosis of atopic dermatitis with total Serum IgE greater than 200 units/ml.

Patients may be of any age or may be children, for example aged 6 months to 5 years. Patients may have any level of severity of diagnosed atopic dermatitis, or may be selected on the basis of severity, for example those with mild or moderate disease only, those with active disease only (ie not disease in remission), those with severe disease only.

A suitable trial population may, for example, be children aged between 6 months and 5 years with total Serum IgE greater than 200 units/ml.

The clinical trial methodology will follow that recommended by the European Task Force on Atopic Dermatitis (29).

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CLAIMS

1. An emulsion comprising an amphoteric surfactant, an alkoxylated cetyl alcohol and a polar drug.

2. An emulsion according to claim 1 wherein the emulsion is an oil-in-water emulsion.

3. An emulsion according to claim 1 or 2 wherein the drug is an anionic drug.

4. An emulsion according to any one of claims 1 to 3 wherein the amphoteric surfactant is a balanced amphoteric surfactant.

5. An emulsion according to any one of claims 1 to 4 wherein the alkoxylated cetyl alcohol is Procetyl AWS.

6. An emulsion according to any one of claims 1 to 5 wherein the amphoteric surfactant is disodium coacoamphodiacetate or a preparation comprising disodium coacoamphodiacetate.

7. An emulsion according to any one of claims 1 to 6 consisting essentially of:

sorbitan tristearate	0.5 to 5% w/v
glycerol monostearate	0.5 to 5%w/v
light liquid paraffin	1 to 20% w/v
white soft paraffin	1 to 10%w/v
iso propyl myristate	0.5 to 5% w/v

drug	0.1 to 20% w/v
disodium edetate	0.01 to 1% w/v
amphoteric surfactant	0.1 to 10% w/v
alkoxylated cetyl alcohol	0.1 to 10% w/v
triclosan	0.01 to 1% w/v
benzyl alcohol	0.01 to 1% w/v
purified water	to 100% v/v of the emulsion

8. An emulsion according to any one of claims 1 to 7 wherein the drug is sodium cromoglycate or nedocromil sodium.

9. A stable oil-in-water emulsion comprising sodium cromoglycate, wherein when the emulsion is applied to skin an amount of sodium cromoglycate penetrates the skin that is sufficient to produce a demonstrable effect in the treatment of atopic dermatitis/eczema.

10. A method of treatment of a skin disease or condition wherein a drug is applied to the skin of an individual affected by the disease or condition in a formulation comprising alkoxylated cetyl alcohol and/or an amphoteric surfactant.

11. Use of an alkoxylated cetyl alcohol and/or an amphoteric surfactant in the manufacture of a medicament for the treatment of a skin disease or condition.

12. A method of treatment of a skin disease or condition comprising applying an emulsion according to claim 8 or 9 to the skin of an individual affected by the disease or condition.

13. Use of an emulsion according to claim 8 or 9 in a method of treating a skin disease or condition.

14. Use of an emulsion according to claim 8 or 9 in the manufacture of a medicament for the treatment of a skin disease or condition.

15. Use according to claim 13 or 14 wherein the disease or condition is one in which skin mast cells and/or delayed (cellular) hypersensitivity reactions and/or inflammation is thought to be involved.

16. Use according to any one of claims 13 to 15 in which the disease or condition is atopic dermatitis or eczema, contact sensitivity, psoriasis, drug sensitivity reactions, apthous ulcers, Behçet's syndrome, pemphigus, urticaria, urticaria pigmentosa, pyroderma gangrenosum, chronic skin ulcers, ulcers associated with Crohn's disease, burns, insect stings/bites, herpetic infections, systemic sclerosis (systemic scleroderma), morphoea (circumscribed or localised scleroderma), dermal nodular fibrosis or sunburn.

17. The emulsion of any one of claims 1 to 9 packaged in a tube, tub, bottle or pressurised aerosol container.

18. An emulsion according to any one of claims 1 to 9 for use in medicine.

ABSTRACT

An oil-in-water emulsion comprising an amphoteric surfactant, alkoxylated cetyl alcohol and a polar drug. The drug may be sodium cromoglycate or nedocromil sodium. The emulsion may be useful in the treatment of skin disease such as atopic dermatitis.